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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,748	03/13/2006	Claas Junghans	JUNGHANS	9385

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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,748	JUNGHANS ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *4,5 and 13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2005* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03-30-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Applicant's response to the restriction requirements of 04/11/2008 has been entered. Claim status. Claims 1-20 are currently pending. Applicant's election of Group I, drawn to claims 1-12, in the response filed on 04/11/2008 is acknowledged. Additionally, Applicant's election **with traverse** of SEQ ID No. 5 is acknowledged. Furthermore, Applicant's election of the following species: peptides comprising the sequence PKKKRKV, as recited in claim 11, is acknowledged.

Response to arguments

Upon further consideration, the examiner **withdraws** the species restriction requirement between peptides composed of three to 30 amino acids as recited in claim 10, and peptides comprising the sequence PKKKRKV as recited in claim 11, because a search of prior art of both species together would be overlapped, and there is not undue burden doing a search for both species together

In addition, Applicant's arguments in view of the official restriction/election requirements of 03-11-2008, in relation to restriction of nucleotides sequences, have been respectfully reconsidered and are found persuasive. That is because SEQ ID NO: 5 encoding a mutated codon optimized *gag* gene, SEQ ID NO: 7 encoding a mutated codon optimized *env*-gp85 gene and SEQ ID NO: 8 encoding a mutated codon optimized *env*-gp70 gene are all components of the same DNA expression vector. However, each one of these sequences encodes for distinct components of the DNA expression vector and is claimed in the alternative. Accordingly, SEQ ID NO: 5, SEQ ID NO: 7 and SEQ ID NO: 8 are examined as independent or distinct species rather than groups because each species is drawn to unique structures with different

physiological functionalities, e.g., antibodies raised against immunogenic epitopes of *env*-gp85 represented by SEQ ID No. 7 won't cross react against immunogenic epitopes of the gag represented by SEQ ID No. 5.

Accordingly, claims 13-20 are withdrawn for further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, and claims 4 and 5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

Therefore claims 1-3 and 6-12 are examined on the merits to which the following grounds of rejection are applicable.

Information Disclosure Statement

The information disclosure statement filed on March 30, 2006 has been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copy. References WO 03/03147 A2 and WO/21322 have been considered to the extent that an English abstract has been provided.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified German untranslated copy of the foreign application 102 44 863.9 has been filed on 03-22-2005.

Notice To Comply With Sequence Rules For Patent Applications Containing nucleotide Sequence And/Or Amino acid Sequence Disclosures

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 through 1.825. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

Specifically the application fails to comply with CFR 1.821(d), which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence **by use of the sequence identifier, preceded by "SEQ ID NO:"** in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application [emphasis added].

In particular, all the nucleotides and proteins sequences in the claims and throughout the specification as filed are described or named with improper identifiers, for example, a sequence identifier for sequence ID NO:5 should be abbreviated as SEQ ID NO:5 and not Seq.ID5 as disclosed on claim 3 and page 13.

Full compliance with the sequence rules is required in response to this Office Action. A complete response to this office action should include both compliance with the sequence rules, which include amendment of the specification and claims to include SEQ ID NOS., and a response to the rejections set forth below. Failure to comply with **both** these requirements in the time period set forth in this office action will be held non-responsive.

Additionally, the following items are required:

There is not submission of a statement indicating that the content of the paper and

computer readable copies are the same, as required by 37 CFR 1.821 (e) or 37 CFR 1.821 (f) or 37 CFR 1.821 (g) or 37 CFR 1.821 (b) or 37 CFR 1.821 (d).

Claim objection

Claims 1-3 and 6-12 is objected to because of the following informalities: Claims 1-3 and 6-12 are grammatically incorrect because the lack indefinite or definite articles, as appropriated, at the beginning of each sentence. Appropriate correction is required.

Claim 1 is objected to because of the following informalities: Claim 1, at line 11, recites the phrase "but not identical" twice. Appropriate correction is required.

Claim 8 is objected to because of the following informalities: Claim 8, at line 5 recites the phrase " and where **the single strands** forming the double strand are linked". The is not antecedent bases in the sentence for "the single strands". Appropriate correction is required.

Specification objection

The Specification is objected because of the use of hyperlinks and other forms of browser-executable code. Some of the pages including hyperlinks are: page 20, i.e., (http://www.kazusa.or.ip/codon/) and page 25, i.e., http://www.fruitfly.org/seg tools/.html. 37 CFR 1.57(d) states that incorporation by reference by hyperlink or other form of browser executable code is not permitted. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See 37 CFR 1.57(d) and MPEP § 608.01(p).

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 1 and dependent claims 2, 3 and 6-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language.

Claims 1 and 2 use parentheses to comment on or qualify part of the sentences. It is unclear whether the limitations in parentheses are meant to be limitations in the claims or whether they are only suggestions/examples. As such, the metes and bounds of the claims cannot be determined. Claims 3 and 6-12 are also included in the rejection as they directly or indirectly depend on claim 1.

Claims 1 and 12 recite the term "and/or". It is unclear what the metes and bounds of this term, as "and" could be interpreted to include only an original structural protein, or all structural and membrane proteins, or, "or" would imply that the cell types are in the alternative. Appropriate correction is required. Claims 2, 3 and 6-11 are also included in the rejection as they directly or indirectly depend on claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 6, 8 and 12 are rejected under 35 USC. 102(b) as being anticipated by Khan et al., al., US 6,248,582 (Date of Patent June 19, 2001).

Khan et al., teaches expression cassettes encoding truncated forms of the Feline leukemia (FeLV) proviral DNA, including mutated forms of the *gag* and *env* genes (col. 2, lines 45-55; col. 3, lines 1-15). In addition, Khan et al., discloses nucleic acid sequences encoded by the plasmid DNA vectors substantially identical to the FeLV proviral DNA, (col. 5, lines 40-65) comprising well known genetic modifications, e.g., insertions, substitutions, deletions and others (col. 8, lines 38-51). Khan et al., does not explicitly teach that plasmid vectors comprise no acceptor sequences, however, the absence of splice donor and acceptor sites is intrinsically necessary on any primary transcript expressing a variant of the Gag and/or env protein as demonstrated by the generation of antibodies specific to expressed truncated forms of said peptides after cat inoculation (col. 14, lines 5-40, Table Tables 1-3) (Current **claims 1, 2 and 6**). Moreover, Khan et al., discloses plasmid DNA expressing truncated forms of the FeLV proviral DNA under the control of the cytomegalovirus (CMV) early promoter region on the 5' end of the genome and a poly A addition signal at the 3' end of the genome to terminate viral mRNA synthesis (col. 3, lines 3-10). Note that plasmid DNA encoding mutated forms of the FeLV polypeptides necessarily and inevitably present double strands consisting of single strands of linked deoxyribonucleotides (Current **claim 8**). Furthermore, Khan et al., discloses that polypeptides or nucleic acids of the invention can be used in pharmaceutical and vaccine compositions (col. 9, lines 20-24) (Current **claim 12**).

Thus by teaching all the claims limitations, Khan et al., anticipates the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khan et al., US 6,248,582 (Date of Patent June 19, 2001) in view of Schirmbeck et al., (J Mol Med. 2001; pp. 343-50).

Khan et al., teaches expression cassettes encoding truncated forms of the Feline leukemia (FeLV) proviral DNA, including mutated forms of the *gag* and *env* genes (col. 2, lines 45-55; col. 3, lines 1-15). In addition, Khan et al., discloses nucleic acid sequences encoded by the plasmid DNA vectors substantially identical to the FeLV proviral DNA (col. 5, lines 40-65)

comprising well known genetic modifications, e.g., insertions, substitutions, deletions and others (col. 8, lines 38-51) wherein expression of the proviral DNA is under the control of a CMV early promoter and a poly A addition termination signal (col. 3, lines 3-10). Khan et al., does not explicitly teach that plasmid vectors comprise no acceptor sequences, however, the absence of splice donor and acceptor sites is implicitly necessary on any primary transcript expressing a variant of the Gag and/or env protein as demonstrated by the generation of antibodies specific to truncated forms of said peptides after cat inoculation (col. 14, lines 5-40, Table Tables 1-3). Furthermore, Khan et al., discloses that the FeLV variants can be modified to improve therapeutic efficacy and lessening the severity or occurrence of side effects during therapeutic use, for example, the nucleotide sequences can be modified to generate fusion proteins comprising the FeLV polypeptides fused to various heterologous proteins (col. 8 lines 49-51, 55-64).

Khan et al., does not specifically teach DNA expression cassettes linked to the peptide sequence PKKKRKV.

However, at the time the application was filed, Schirmbeck et al., discloses a minimalistic immunologically defined gene expression vector (MIDGE) consisting of covalently closed linear DNA molecules with a linear double-strand region, wherein the single strands forming the double strands are linked by short single-strand loops of DNA and consist only of the antigen-coding sequence under the control of an operable promoter in the animal to be vaccinated and a terminator sequence (p. 344, col. 1, last paragraph). Moreover, Schirmbeck et al., teaches that said vectors are covalently linked with the nuclear localization peptide of SV40 comprising the sequence PKKKRKVEDPYC and said vectors also code for the small surface antigen of

hepatitis B (hepatitis B small surface antigen HBsAG). Furthermore, Schirmbeck et al., describes the use of the vector for the production of a vaccine (p. 346, col. 1, paragraph 2-3). The author states the following benefits: " (a) the elimination of bacterial DNA sequences that will reduce unfavorable side effects and (b) the conjugation of NLS peptides to MIDGE constructs that increases transfection efficacy and priming of immunity. MIDGE vectors are thus attractive candidates for DNA vaccines to efficiently prime humoral and cellular antiviral immunity" (p. 349, col. 2, last paragraph).

Therefore, in view of the benefits of enhancing the production antibodies and enhancing the cellular immune response by using oligonucleotide delivery based on a single nuclear localization peptide derived from the SV40 large-T antigen comprising the sequence PKKKRKVEDPYC covalently attached to the expression vector construct as taught by **Schirmbeck** et al., it would have been *prima facie* obvious to replace the nucleic acid sequence coding for the small surface antigen of hepatitis B in a MIDGE vector for any of other DNA sequence encoding truncated FeLV polypeptides. The manipulation of previously identified DNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology. One of ordinary skill in the art would have had a reasonable expectation of success in generating a DNA construct for the expression of gene products of the FeLV comprising one or more peptides including the sequence PKKKRKV to achieve the predictable result of inducing an efficient humoral and cellular immune response in a composition comprising said vector used to vaccinate cats given the results of both Khan and **Schirmbeck** demonstrating the success of the methodology and materials detailed in each of the disclosures. The references above provide all the elements of gene expression vector (MIDGE) comprising a

one or more peptides including the sequence PKKKRKV liked to said vector to anticipate claims 1, 9-11.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Khan et al., US 6,248,582 (Date of Patent June 19, 2001) in view of Schirmbeck et al., (J Mol Med. 2001 ; pp. 343-50) as applied to claims 1, 9-11 above and further in view of Shiver et al., (US Patent. 6,696,291 (Date of Patent Feb. 24, 2004), Laprevotte et al., (1984, J. Virol. , pp. 884-894 ; Genbank Accession No., K01803, FeLV gag cDNA) and Gardner-Arnstein feline leukemia oncovirus codon usage (www.kazusa.or.ip/codon, of record).

The combined references of Khan and Schirmbeck fail to teach a DNA expression construct containing a gag optimized nucleotide sequence of SEQ ID No. 5.

However, at the time the application was filed, Shiver discloses synthetic DNA molecules encoding HIV gag which codons include the projected host cell's preferred codons (col. 7, lines 55-60). Moreover, Shiver teaches that codon preference phenomena on recombinant DNA techniques are manifest, and the phenomenon may serve to explain many prior failures to achieve high expression levels of exogenous genes in successfully transformed host organisms (col. 7, lines 13-19). Specifically, Shiver teaches optimized *env* and *gag* genes of HIV (IIIB, MN or CAM-1) to construct vectors for use as vaccines (col. 16, paragraph 2). The design of synthetic gene segments resulting in increased Gag expression are disclosed in Example 3, lines 24-57, including selection codons for observed frequency of use by human genes that remove the constraints on expression of Gag. Shiver teaches that the methods were used to generate the synthetic gene segments for HIV Gag creating a gene comprised entirely of optimal codon usage for expression in the host organism , e.g., human subject (col. 18, lines 58-61; Example 4, HIV-1

gag comprising optimal codons). Furthermore, Shiver teaches that a person in need of therapeutic or prophylactic immunization against infection with human immunodeficiency virus is injected with HIV DNA encoding all or part of the *env, gag* or *pol* genes or combinations thereof (col. 23, lines 1-2).

Shiver et al, do not teach specifically codon preferences of *env* and *gag* genes of FeLV for expression in cats.

However, at the time the invention was made, the complete genome of the *gag* gene of FeLV comprising the instantly disclosed sequence of SEQ ID NO: 5 was well known in the art as evidence by the publication of Laprevotte et al. Additionally, feline leukemia oncovirus codon usage as exemplified by the disclosure of www.kazusa.or.ip/codon was well known in the art.

Therefore, in view of the benefits of codon usage achieving high expression levels of exogenous *gag* and *env* HIV-1 genes in successfully transformed host organisms as taught by Shiver, it would have been *prima facie* obvious to optimize the wild type FeLV nucleotide sequence as disclosed by Laprevotte et al., coding for FeLV *gag* and *env* proteins according to the most prevalent codons highly expressed in cat genes as taught by Gardner-Arnstein feline leukemia oncovirus codon usage (kazusa.or.ip/codon). The motivation to combine the references is provided by Shiver because he teaches that codon optimization improves the efficiency of gene expression in host organisms. Further, based on the detailed teachings of the Khan, Schirmbeck, Shiver's Patent, Laprevotte, and Gardner-Arnstein feline leukemia oncovirus codon usage and the high level of skill in the art of molecular cloning, the skilled artisan would have had a reasonable expectation of success in generating a DNA expression vector containing the optimized gag nucleotide sequence of SEQ ID No. 5 in order to potentiate the immune response

to the expressed antigen and to enhance the therapeutic benefit to the host, as encompassed the instant claims. The references above provide all the elements of an expression construct containing a gag optimized nucleotide sequence of SEQ ID No. 5 to anticipate claim 3.

Conclusion

Claims 1-3 and 6-12 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633